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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: USE OF NEFOPAM FOR THE TREATMENT OF NAUSEA OR EMESIS

(57) Abstract: The invention relates to the use of nefopam for the manufacture of a medicament for the treatment of nausea, dizzi-  
ness, blurred vision and emesis.

WO 03/105832 A1

USE OF NEFOPAM FOR THE TREATMENT OF  
NAUSEA OR EMESISField of the Invention

This invention relates to the use of a known compound in the treatment of emesis and related conditions.

5 Background of the Invention

Nefopam is a centrally acting non-narcotic analgesic not structurally related to other analgesics. Nefopam has been shown to induce antinociception in animal models of pain and in humans (reviewed in Heel *et al.*, Drugs 19(4): 249-67, 1980). However, nefopam is not active in the mouse tail-flick test, the hot  
10 plate test or the Randall-Selitto pressure test in rats (Conway and Mitchell, Arch. Int. Pharmacodyn. Ther. 226(1): 156-71, 1977), suggesting that its analgesic mechanism is not opiate-like or anti-inflammatory in nature. Nefopam's antinociception is not blocked by nalaxone, further suggesting that its analgesic action is not through opiate receptors.

15 *In vitro* and *in vivo* studies with nefopam enantiomers have shown that (+)-nefopam has more potent analgesic and dopamine, norepinephrine and serotonin-uptake inhibitory properties than (-)-nefopam, with the order of potency given as (+)-nefopam > (±)-nefopam > (-)-nefopam (Fasmer *et al.*, J.Pharm. Pharmacol. 42(6): 437-8, 1987; Rosland and Hole, J. Pharm. Pharmacol. 42(6):  
20 437-8, 1990; Mather *et al.*, Chirality 12(3): 153-9, 2000). Mather *et al.* (2000) conclude that "...there is currently no compelling rationale to justify administering or monitoring individual enantiomers [of nefopam]".

Nefopam has also been shown to be opiate-sparing when given with morphine in trials of patient-controlled analgesia (Mimoz *et al.*, Anaesthesia  
25 56(6): 520-5, 2001).

Conventional release preparations of nefopam have been commercially available for many years, for use in treating moderate to severe pain. However, the short elimination half-life of nefopam (four hours) means that it is difficult to maintain analgesic efficacy over the normal dosing period (three times daily).  
30 Dose escalation of nefopam brings about an increase in the frequency of adverse drug reactions associated with the analgesic, and adverse effects on pulse and blood pressure have been observed following parenteral delivery of

therapeutic doses of nefopam (Heel *et al.*, 1980). Chronotropic and ionotropic effects on the heart are not present when nefopam is administered orally (Bhatt *et al.*, Br. J. Clin. Pharmacol. 11(2): 209-11, 1981).

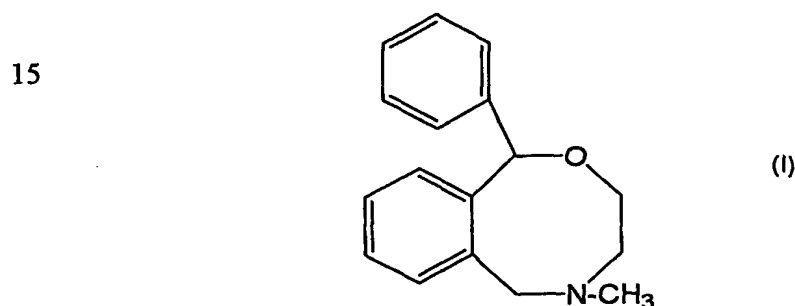
5 Nausea and vomiting are side-effects of the use of many drugs, including those administered for the treatment of pain.

### Summary of the Invention

According to the present invention, emesis or a related condition is treated by the use of nefopam. Given nefopam's side-effect profile, it was surprising to find that racemic nefopam and its enantiomers were able to prevent  
10 or diminish emesis caused by administration of opioid and other recognised pro-emetic agents.

### Description of Preferred Embodiments

As used herein, "nefopam" refers to a compound of formula I



and salts, e.g. the hydrochloride, metabolites and prodrugs thereof, as well as the (+) and (-) enantiomers which are as far as possible optically pure. (+)-Nefopam may be preferred, for reduced side-effects caused by interaction.

According to the invention, nefopam is used to treat nausea, dizziness,  
25 blurred vision or emesis, including, but not limited to, acute, delayed, post-operative, last-phase and anticipatory emesis. This condition may be induced by, for example, chemotherapy, radiation, toxins, pregnancy, alcohol withdrawal, nicotine withdrawal, drug withdrawal, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal motility,  
30 dysmenorrhoea, visceral pain, migraine, increased intracranial pressure, decreased intracranial pressure, depression or opioid analgesics. In addition, nefopam may be used to treat emesis caused by certain drugs such as

antidepressants (examples including amitriptyline, imipramine, desipramine, venlafaxine, citalopram, trazadone, paroxetine, nefazodone, fluoxetine and (S)-citalopram), anticonvulsants (examples including lamotrigine, gabapentin and carbamazepine), antipsychotics (examples including clozapine, chlorpromazine, fluphenazine, haloperidol and loxapine), anxiolytics (examples including buspirone and lorazepam), anti-Parkinson's agents (examples including apomorphine, pergolide, levodopa, dopamine, naxagolide, bromocriptine and amantadine), CNS stimulants (examples including dexamphetamine and methylphenidate), opioids (examples including morphine, fentanyl, buprenorphine, codeine, methadone, oxycodone, phenacozine and diamorphine), and anticancer agents (examples including cisplatin, aldesleukin, altretamine, carboplatin, carmustine, cyclophosphamide, cytarabine, decarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, fluorouracil, idarubicin, ifosfamide, irotecan, lomustine, mechlorethamine, melphalan, methotrexate, mitoxantrone, pentostatin, procarbazine and streptozocin).

Nefopam may be used according to the invention when the patient is also being given another anti-emetic agent. Such agents include phenothiazines, 5HT<sub>3</sub> receptor antagonists, dopamine antagonists, anticholinergic agents, anti-histamines, histamine analogues, cannabinoids, corticosteroids, GABA receptor antagonists, NK<sub>1</sub> receptor antagonists, and  $\alpha_2$  and  $\alpha_3$  adrenoceptor antagonists.. Specific examples of these types of compounds are cyclizine, dolasetron, granisetron, ondansetron, tropisetron, nabilone, scopolamine, cinnarizine, promethazine, betahistine, dexamethasone, methylprednisolone, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, thiethylperazine, droperidol, domperidone and haloperidol..

Any suitable route of administration can be used. For example, any of oral, topical, ocular, rectal, vaginal, inhalation and intranasal delivery routes may be suitable. The dose of the active agent will depend on the nature and degree of the condition, the age and condition of the patient, and other factors known to those skilled in the art. A typical dosage is 10-100 mg given one to three times per day.

The evidence upon which this invention is based follows.

## Study

Male ferrets ( 0.9- 1.7 kg) obtained from Leeds University were housed in pairs at  $22 \pm 1^\circ\text{C}$  and had free access to food ( SDS Diet 'C' (E), Special Diet Services, UK) and water. They were housed under artificial lighting with lights  
5 on between 07:00 and 21:00 hours. For experimental use, animals were removed from their holding cages and placed individually into observation cages. The animals were allowed free access to water and food. The animals were divided into separate groups of 4 animals per group.

Animals were frequently observed throughout the experiments by a  
10 trained technician to ensure that the animals remained in good health. In addition, animal behaviour was video recorded for subsequent analysis of emesis (see Rudd et al., 1994). Emesis was characterized by rhythmic abdominal contractions which were either associated with the oral expulsion of solid or liquid material from the gastrointestinal tract (i.e. vomiting) or not  
15 associated with the passage of material (i.e. retching movements). The number of highly distinctive abdominal contractions was counted.

(+)-Nefopam was dissolved in saline and administered in a volume of 1 ml/kg. Normal saline was used as the control vehicle injection. Cisplatin (Cisplatin Injection Sterile Concentrate 50 mg/ 50ml; Onco-Tain: Faulding  
20 Pharmaceuticals PLC. Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW,UK) was administered in a volume of 5 ml / kg i.p.

Ferrets (n=4) were pre-dosed intraperitoneally with either racemic nefopam (1, 3 and 10 mg/kg i.p. - Figure 1a), (-)-nefopam (10 and 30mg/kg – Figure 1b) or (+)-nefopam (0.3, 1 and 3mg/kg – Figure 1c) one hour prior to  
25 being given an emetic dose of morphine (0.125mg/kg s.c.). Observations were recorded over a 4hr period post-morphine dosing and scored for incidences of retching and vomiting. Results are shown in Figure 1.

(+)-Nefopam (3mg/kg) was administered to ferrets (n=4) intraperitoneally three times daily (q8h) starting one day before cisplatin administration (5 mg/kg  
30 i.p.) and continuing for three days after cisplatin administration. Observations were recorded over the 72hr period post-cisplatin dosing and scored for incidences of retching and vomiting. Results are shown in Figure 2.

CLAIMS

1. Use of nefopam for the manufacture of a medicament for use in the treatment of a condition selected from nausea, dizziness, blurred vision and emesis.
- 5 2. Use according to claim 1, wherein the condition is acute, delayed, post-operative, late-phase or anticipatory emesis.
3. Use according to claim 1 or claim 2, wherein the condition is associated with dysmenorrhoea, migraine, cancer or other pain condition.
4. Use according to claim 1 or claim 2, wherein the condition is induced by  
10 one or more of radiation, toxins, pregnancy, alcohol withdrawal, nicotine withdrawal, drug withdrawal, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal mobility, visceral pain or increased or decreased intracranial pressure.
5. Use according to any preceding claim, wherein the condition is drug-  
15 induced.
6. Use according to claim 5, wherein the condition is induced by chemotherapy.
7. Use according to claim 5 wherein the condition is induced by an opioid analgesic.
- 20 8. Use according to any preceding claim, wherein the patient is also administered another agent that has anti-emetic properties.
9. Use according to claim 8, wherein said agent is selected from phenothiazines, 5HT<sub>3</sub> receptor antagonists, dopamine antagonists, anticholinergic agents, anti-histamines, histamine analogues, cannabinoids,  
25 corticosteroids, GABA receptor antagonists, NK1 receptor antagonists, and  $\alpha_2$  and  $\alpha_3$  adrenoceptor antagonists.
10. Use according to claim 8, wherein said agent is selected from cyclizine, dolasetron, granisetron, ondansetron, tropisetron, nabilone, scopolamine, cinnerizine, promethazine, betahistine, dexamethasone, methylprednisolone,  
30 metoclopramide, chlorpromazine, perphenazine, prochlorperazine, thiethylperazine, droperidol, domperidone and haloperidol.

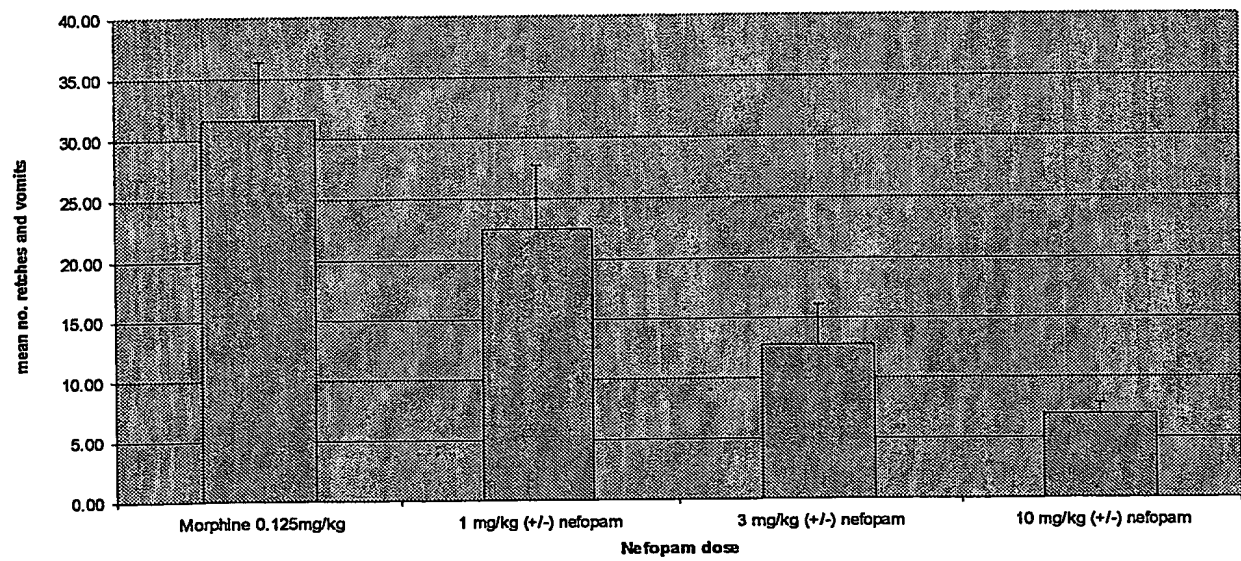


Fig. 1a

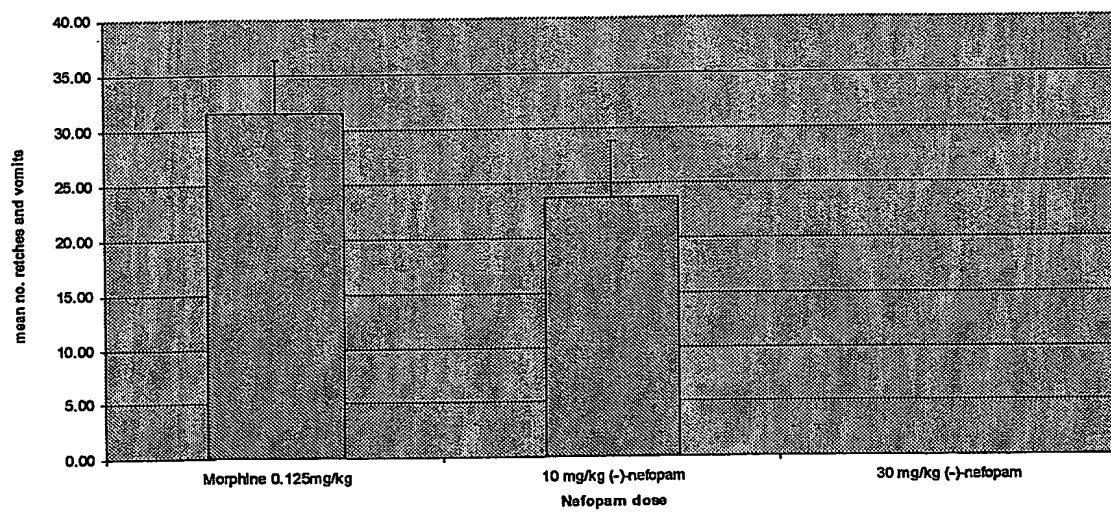


Fig. 1b

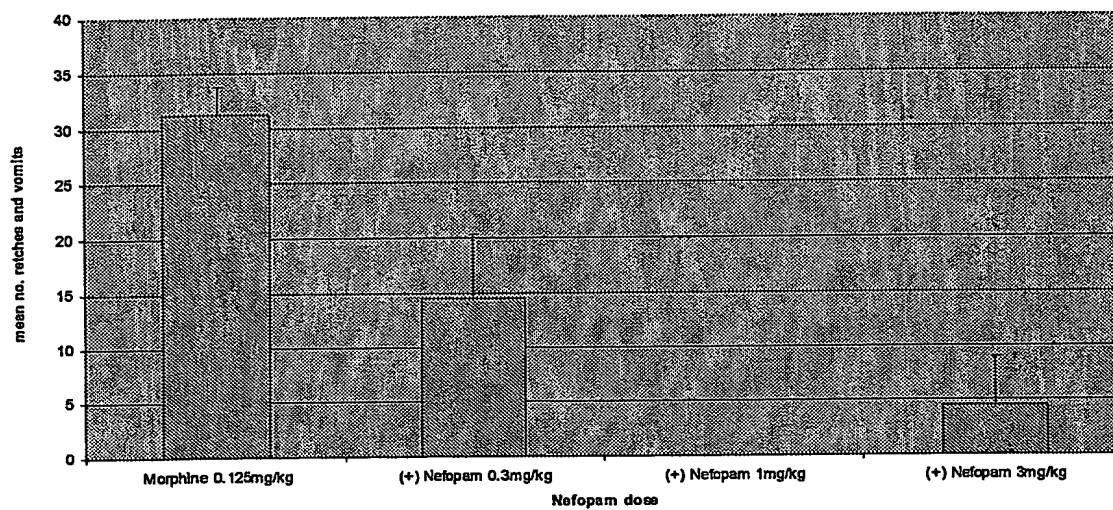


Fig. 1c

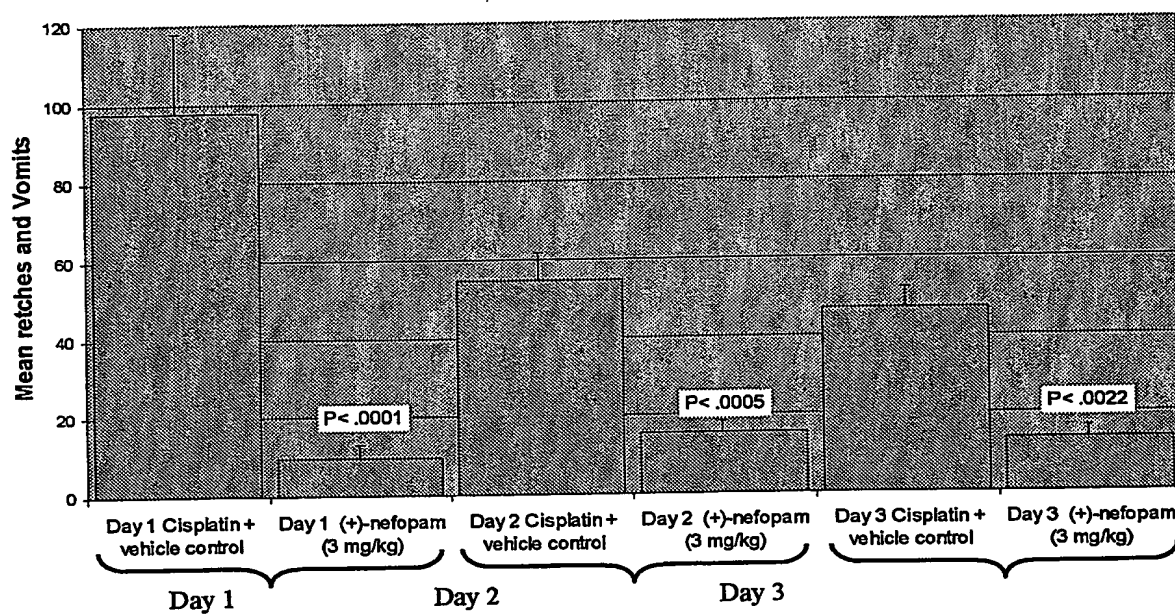


Fig. 2

# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/395 A61P1/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS, EMBASE, PASCAL, SCISEARCH, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BENHAMOU D (REPRINT): "Nefopam and combined analgesics"</p> <p>ANNALES FRANCAISES D ANESTHESIE ET DE REANIMATION, (DEC 2002) SP. ISS. SI, PP. 9-14. PUBLISHER: EDITIONS SCIENTIFIQUES MEDICALES ELSEVIER, 23 RUE LINOIS, 75724 PARIS CEDEX 15, FRANCE. ISSN: 0750-7658., XP009017788</p> <p>Hop Bicetre, Dept Anesthesie Reanimat, AP HP, 78 Ave Gen Leclerc, F-94270 Le Kremlin Bicetre, France (Reprint); Hop Bicetre, Dept Anesthesie Reanimat, AP HP, F-94270 Le Kremlin Bicetre, France</p> <p>the whole document in particular page 10, right-hand column, paragraphs 2,3 page 11 figures 2,3 page 12, left-hand column</p> <p>-/-</p>	1-5,7

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

24 September 2003

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## INTERNATIONAL SEARCH REPORT

PCT/GB 03/02586

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>-----</p> <p>MIMOZ O ET AL: "Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection."  ANAESTHESIA. ENGLAND JUN 2001,  vol. 56, no. 6, June 2001 (2001-06), pages 520-525, XP009017735  ISSN: 0003-2409  abstract  table 4  page 524, right-hand column, line 32-34</p>	1-5,7
X	<p>-----</p> <p>MOFFAT A C ET AL: "Postoperative nefopam and diclofenac. Evaluation of their morphine-sparing effect after upper abdominal surgery"  ANAESTHESIA 1990 UNITED KINGDOM,  vol. 45, no. 4, 1990, pages 302-305, XP009017736  ISSN: 0003-2409  abstract  page 302, left-hand column, paragraph 2  page 303, left-hand column, paragraphs 2,3  page 303, right-hand column, paragraph 3</p>	1-5,7-10
X	<p>-----</p> <p>PILLANS P I ET AL: "Adverse reactions associated with nefopam."  THE NEW ZEALAND MEDICAL JOURNAL. NEW ZEALAND 22 SEP 1995,  vol. 108, no. 1008,  22 September 1995 (1995-09-22), pages 382-384, XP009017734  ISSN: 0028-8446  abstract</p>	1-4
X	<p>-----</p> <p>GHOSE K ET AL: "An open pilot study of the preventive effect of nefopam in migraine headaches"  HEADACHE QUARTERLY 1999 UNITED STATES,  vol. 10, no. 3, 1999, pages 221-224, XP009017751  ISSN: 1059-7565  the whole document</p>	1-4
A	<p>-----</p> <p>LASSETER K C ET AL: "Nefopam HCl interaction study with eight other drugs"  JOURNAL OF INTERNATIONAL MEDICAL RESEARCH 1976,  vol. 4, no. 3, 1976, pages 195-201, XP009017739  abstract  figure 3</p>	